



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>3</sup> :</b>  <b>A61K 37/26</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 83/ 00288</b>  <b>(43) International Publication Date:</b> 3 February 1983 (03.02.83)
<b>(21) International Application Number:</b> PCT/DK82/00068 <b>(22) International Filing Date:</b> 16 July 1982 (16.07.82) <b>(31) Priority Application Number:</b> 3198/81 <b>(32) Priority Date:</b> 17 July 1981 (17.07.81) <b>(33) Priority Country:</b> DK <b>(71) Applicant (for all designated States except US):</b> NOR-DISK INSULINLABORATORIUM [DK/DK]; Niels Steensensvej 1, DK-2820 Gentofte (DK). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> BALSCHMIDT, Per [DK/DK]; Tibberup alle 20, DK-3060 Espergærde (DK). JOHANSEN, Kristian, Betton [DK/DK]; Gurtevej 161 B, DK-3000 Helsingør (DK). <b>(74) Agent:</b> HOFMAN-BANG & BOUTARD; Adelgade 15, DK-1304 København K (DK).		<b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i> <i>With amended claims and statement.</i> <i>In English translation (filed in Danish).</i>
<b>(54) Title:</b> A STABLE AQUEOUS, THERAPEUTIC INSULIN PREPARATION AND A PROCESS FOR PREPARING IT		
<b>(57) Abstract</b>  <p>The insulin preparation, which is suitable for use in insulin delivery devices, consists of an insulin-containing aqueous medium having a pH of 6.5 to 9 and a polyoxyethylene alkylether of the general formula <math>R - O - (CH_2 - CH_2 - O)_n - H</math> wherein R represents a straight or branched, saturated or unsaturated <math>C_8 - C_{15}</math> alkyl group, and n is an integer from 2 to 25, and, if desired, common additives, such as isotonic, preservatives, buffers, etc., and optionally also a component causing the effect of the preparation to be accelerated or protracted. The preparation is prepared by admixing an aqueous medium containing human or animal insulin or a derivative thereof with a polyoxyethylene alkylether, and if necessary, adjusting the pH of the medium to 6.5 to 9, and if desired, adding any residual components of the medium and/or adjusting the insulin concentration to provide the finished preparation. After more than 500 hours' of constant shaking in the presence of atmospheric air in 3/4 filled vials, disposed horizontally, at 37°C with 80 oscillations per minute, such preparations are still clear and without physical or chemical conversions.</p>		

A stable aqueous, therapeutic insulin preparation and a process for preparing it

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- 5 The present invention relates to a novel stable therapeutic insulin preparation in an aqueous medium suitable for use in insulin delivery devices, including portable devices for external as well as internal use.
- 10 It is generally held that most of the complications that may arise in connection with an insulin-dependent diabetes can be ascribed to inadequate control of the glucose content in the blood (Tehobroutsky, Diabetologia, 15, 143-152 (1978)). In the conventional insulin therapy, insulin
- 15 is administered to the diabetic by way of one to three injections per day, resulting in a fluctuating insulin and glucose content in the blood. In contrast, the non-diabetic constantly receives insulin from his pancreas, secreted in the blood stream and in an amount adapted to
- 20 his needs.

In recent years efforts have therefore been concentrated on the development of insulin delivery devices which can remedy the above-mentioned problem. If, however, such

25 devices are applied internally or externally to a human, insulin preparations experience far inferior storage conditions in terms of temperature and motion when stored in the reservoir of the device than the injectable preparations. The previously known insulin preparations are

30 intended for storage at rest at 4°C. In contrast, the insulin preparation is stored in the reservoir of insulin devices for an extended period of time at temperatures between 30 and 37°C, and is moreover subjected to a good deal of motion during this period.

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It is known that insulin in solution is adsorbed to hydro-



phobic interfaces, including interfaces between aqueous solution and air (Weisenfeld et al., Diabetes 17, 766 (1968)). The insulin thus adsorbed can denature, and aggregation can also take place. Then, these aggregates  
5 of denatured insulin are desorbed from the interface, and they sediment and form a precipitate at a sufficiently high concentration in the solution. These processes are accelerated by increasing temperatures and motion.

10 Thus, it is not to be wondered at that it has turned out that in the use of the conventional dissolved insulin preparations in delivery devices, the supply tubes, valves and filters of the system are often gradually blocked by precipitated insulin aggregates, and that the  
15 desired very precise dosing of the insulin into the blood stream is prevented by this. These problems of aggregation have been discussed in great detail by W.D. Loughheed et al., Diabetologia 19, 1-9 (1980), reporting that the varying tendency to aggregation may be attributable to  
20 temperature, ion concentration and type, pH value, presence of carbon dioxide and other gases, as well as other factors.

It has been found for conventional insulin preparations  
25 that the quality of the insulin reaching the blood stream after an extended stay in a delivery device with associated reservoir is significantly inferior to the quality after storage and use under the common conditions. This, too, is understandable because of the aggregation  
30 and/or formation of denatured insulin which takes place during the storage in the reservoir of the delivery device.

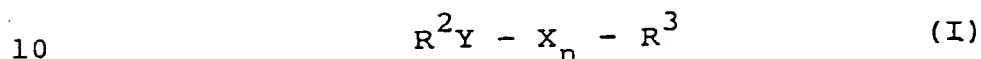
Thus, it is not possible with the combination of delivery  
35 device/conventional insulin preparation to solve the problem referred to.



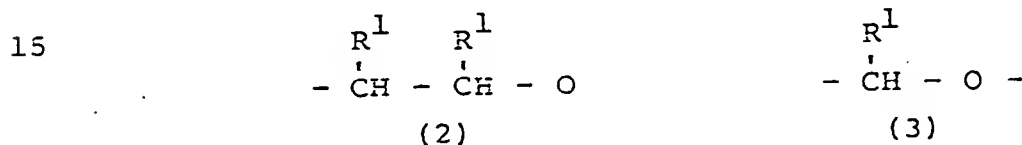
It is proposed in the Danish Application 1851/80, cf.

the EP 18609, relating to denaturation-resistant, aqueous protein solutions, including insulin solutions, to solve the problem by adding to the solution a surfactant

5 having a chain-like basic structure, whose links contain alternating slightly hydrophobic and slightly hydrophilic regions, preferably a homopolymerisate, copolymerisate or block polymerisate of the formula



wherein  $X_n$  represents a chain of  $n$  links of the formulae (2) or (3)



in an arbitrary order, and  $n$  represents 2 - 80, preferably 8-45,

$Y$  represents oxygen or imino,

$R^1$  represents hydrogen, methyl or ethyl, where the groups  $R^1$  may be the same or different, with the proviso that

methyl or ethyl is present in at least half of the chain links  $X$ , and  $R^2$  and  $R^3$  independently represent hydrogen

25 or an organic group, preferably alkyl of 1 to 20 carbon atoms, carboxyalkyl of 2 to 20 carbon atoms or alkyl-phenyl of 1 to 10 alkyl carbon atoms, with the proviso that when  $Y$  represents imino  $R^2$  can only represent alkyl

30 of 1 to 20 carbon atoms. These surfactants "saturate" the interfaces since the hydrophobic groups of the chains bind well to a larger hydrophobic face. However, the hydrophobic regions of the dissolved proteins only present very small faces to which the surfactants do not bind,

35 and for the same reason the proteins cannot bind to the hydrophobic face as long as free surface-active elements

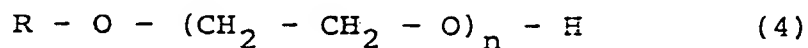


are present in the solution. It is not denied that the protein solutions produced in examples 1-6 possess the properties described in that application, such as stability. But it is quite evident that in connection with insulin solutions the invention does not solve the problems associated with the insulin preparations to be used in delivery devices, and as described in the foregoing. It is noted that examples 7-13 (insulin) do not in fact report any stability, as is the case with examples 1-6. Reproduction of example 11 showed, as stated below, inadequate durability in shaking tests.

It has now surprisingly been found that a narrow group of non-ionic surfactants of the polyoxyethylene alkyl-ether type in extremely low concentrations effectively prevent the denaturations and aggregations that occur if insulin in an aqueous medium is subjected to elevated temperatures while being moved in the presence of air.

Accordingly, the invention relates to a stable aqueous, therapeutic insulin preparation which is particularly useful in insulin delivery devices and is unique in that the aqueous medium has a pH of 6.5 to 9 and contains a polyoxyethylene alkylether of the general formula

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wherein R represents a straight or branched, saturated or unsaturated  $C_8 - C_{15}$  alkyl group, and n is an integer from 2 to 25.

Preferred compounds are in particular those of formula 4 wherein R represents a  $C_{12} - C_{13}$  alkyl group, preferably lauryl or tridecyl, because they give the best stability. n in the compounds of formula 4 is an integer, preferably from 4 to 23, in particular 6 to 15.



These polyoxyethylene alkylethers are active in insulin preparations in an aqueous medium in concentrations down to 2 ppm. The effect for concentrations between 2 and 100 ppm is demonstrated below, but the compounds are also active in higher concentrations, such as 100 to 300 ppm or more, e.g. up to 1000 ppm. The concentration most appropriate in the individual case can be determined by tests and depends e.g. upon the type of the compound, the concentration of insulin and the other components of the medium, as well as upon the mode of application of the preparation.

The above-mentioned compounds are comprised by the general formula for a group of non-ionic surfactants which prevent denaturation of insulin and adsorption to interfaces according to the DE Offenlegungsschrift 29 17 535. The compounds used in accordance with the invention are not described in detail or examined in the examples of that specification, which are included in the EP 18609 claiming priority from this DE application. In the EP 18609, the formula of the active compounds is restricted to formula 1 above. Compounds of the type used in accordance with the invention have directly been characterized as having no protective effect during the processing of the EP 18609 by the EPO in connection with a discussion of the DE Auslegeschrift 26 20 483.

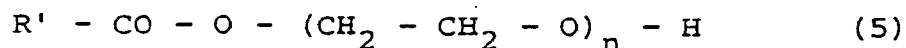
This specification concerns stable aqueous insulin solutions, in particular for nasal administration. The solutions have a pH of 2.5 to 4.7 and contain one or more non-ionic surfactants having an HLB value of 9 to 22 and/or polyethylene glycol having a molecular weight of 200 to 7500 as a stabilizer to counteract the deamidation of the insulin, well-known in the acid pH range, and to improve the shelf-life by counteracting gel formation and precipitations. The content of surfactant



usually constitutes 0.1 to 20% by weight, preferably 0.5 to 10% by weight. A content below 0.1% is characterized as being insufficient.

5 Examples of useful non-ionic compounds are stated to include a large number of types, such as compounds of polyoxyethylene and hydrogenated castor oil, polyoxyethylene fatty acid esters, polyoxyethylenesorbitan fatty acid esters, polyoxyethylenealkylphenyl ethers,  
10 polyoxyethylene-polyoxypropylene alkylethers and finally polyoxyethylene alkylethers of formula 4, in which, however, R may represent  $C_4 - C_{18}$  and  $n = 3$  to 60.

Apart from the fact that the skilled person who realized  
15 the inadequate stabilizing effect by shaking tests with the compounds used in the EP 18609 would not be induced at all to test compounds which are known as stabilizers against deamidation of insulin in acid solutions, he could in particular not predict that precisely the narrow  
20 range of compounds proposed by the present invention would be effective. This is the more surprising as the structurally closely related esters of the formula



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wherein  $R'$  and  $n$  have values corresponding to formula 4, are inactive as stabilizers in shaking tests.

The Zn content in the medium can constitute 0 to 5%,  
30 preferably 0 to 1%, in particular 0.3 to 1% of the insulin, expressed as weight per cent of anhydrous insulin. However, a particularly good effect of the polyoxyethylene alkyl-ethers is obtained when the Zn content in the dissolved insulin constitutes between 0.6 and 0.9%. The pH value  
35 is, as mentioned, between 6.5 and 9.0, but is preferably 6.5 to 8.0, in particular 7.0 to 8.0. The insulin concen-



tration may be up to 1500 IU/ml.

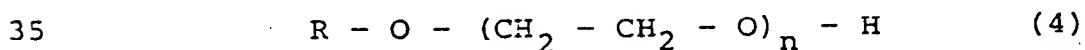
According to the invention, aqueous insulin preparations for the use described can be prepared by the following  
5 general procedure:

Human or animal insulin or biologically active derivatives thereof are dissolved in water with addition of e.g. an HCl solution. The Zn content is adjusted by  
10 adding a solution of a Zn salt in water. The resulting solution is admixed with a solution that may contain a preservative, such as phenol, m-cresol or p-methylhydroxy benzoate; an isotonic, such as glucose, glycerol or sodium chloride, and - to maintain a specific pH - a  
15 buffer such as acetate or sodium phosphate. pH is adjusted to the desired value e.g. with an NaOH solution or an HCl solution. Finally, the stabilizing polyoxyethylene alkylether dissolved in water is added.

20 Optionally, the insulin may be dissolved directly in an aqueous medium containing a buffer, an isotonic, a preservative and the stabilizing compound, and then the Zn content and the pH are adjusted.

25 The order of these steps is arbitrary, it being possible to vary it in different ways; e.g. the stabilizing polymer might be added to the insulin during the purification process of the insulin.

30 Thus, the invention also relates to a process for preparing the present insulin preparations which comprises admixing an aqueous medium containing insulin with a polyoxyethylene alkylether of the formula





wherein R and n are as defined above, and, if necessary, adjusting the pH of the medium to 6.5 to 9, and, if desired, adding any residual components of the medium and/or adjusting the insulin concentration to provide  
5 the finished preparation.

The invention will be illustrated more fully by the following examples.

10 EXAMPLE 1

Crystalline pork insulin corresponding to 100,000 IU containing 0.4% Zn was dissolved in 400 ml of water by means of 3.3 ml of 1N HCl. 10 ml of a  $\text{ZnCl}_2$  solution  
15 were added, containing 2.20 mg of  $\text{ZnCl}_2$  per ml. Then were added 500 ml of a solution of 3.0 g of m-cresol, 16.0 g of anhydrous glycerol and 2.373 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ . After mixing, pH was adjusted to 7.3 by means of 1N NaOH. Addition of 10 ml of a solution containing  
20 1% polyoxyethylene-23-laurylether (corresponding to a concentration of 100 ppm), was followed by topping with water to 1 litre, and the solution was sterile filtrated.

After more than 699 hours' of constant shaking in the  
25 presence of atmospheric air in 3/4 filled vials, disposed horizontally, at  $37^\circ\text{C}$  with 80 oscillations per minute, the preparation was still clear and without physical or chemical conversions.

30 EXAMPLE 2

The procedure was the same as in example 1, but with polyoxyethylene-10-laurylether substituted for polyoxyethylene-23-laurylether.

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A preparation of the same quality as in example 1 was obtained.



EXAMPLE 3

Crystalline pork insulin corresponding to 100,000 IU containing 0.7% Zn was dissolved in 400 ml of water by means of 3,3 ml of 1N HCl. Then were added 500 ml of a solution of 3.0 g of m-cresol, 16 g of anhydrous glycerol and 2.373 g of  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ . After mixing pH was adjusted to 7.3 by means of 1N NaOH. Addition of 1 ml of a solution of 1% polyoxyethylene-15-tridecylether (corresponding to a concentration of 10 ppm) was followed by topping with water to 1 litre, and the solution was sterile filtrated.

After more than 1000 hours' of constant shaking in the presence of atmospheric air in 3/4 filled vials, disposed horizontally, at 37°C with 80 oscillations per minute, the insulin preparation was still clear and without physical or chemical conversions.

20 EXAMPLE 4

The procedure was the same as in example 3, but using polyoxyethylene-6-tridecylether added to insulin solutions in concentrations corresponding to 2 ppm, 5 ppm, 10 ppm, 25 ppm, 50 ppm, and 100 ppm, respectively.

The solutions were subjected to shaking tests like in example 3, and all of them were clear and without physical or chemical conversions after more than 1000 hours' of shaking.

EXAMPLE 5 (Comparative example)

The procedure was the same as in example 1, adding, however, 100 ppm polyoxyethylene-20-cetyler (R =  $\text{C}_{16}$ ) instead of polyoxyethylene-23-lauryler.



Shaking tests like in example 1 demonstrated that the stability only lasted for 137 hours.

EXAMPLE 6 (Comparative example)

5

The procedure was the same as in example 1, adding, however, 100 ppm "Nopalcol L-4", which is a polyoxyethylene-9-laurate, instead of polyoxyethylene-23-lauryl-ether. The solution was cloudy from the beginning and  
10 remained cloudy.

It will be seen from the foregoing examples that the closely related polyoxyalkylene alkylesters are inactive.

15 There is no fixed limit of satisfactory stabilizing effect in the above-mentioned shaking tests. The applicant has set 300 hours as a minimum, internal standard for pump insulin preparations with additives.

20 In view of this it is clear that polyoxyethylene alkylethers of formula 4 in which R is  $C_{16}$  are not satisfactory.

COMPARATIVE EXAMPLE 7

25 (reproduction of example 11 in the EP 18609)

Crystalline pork insulin (40,000 IU) having 0.6% by weight of zinc was dissolved in 200 ml of water with addition of 3 ml of 1N hydrochlorid acid. This solution  
30 was admixed with 700 ml of a solution of 1 g of p-hydroxybenzoic acid methylester, 17 g of glycerol, 1.4 g of sodium acetate, 3  $H_2O$  and 10 mg of linear polypropylene glycol of an average molecular weight of 1.750. The solution was adjusted to a pH of 6.9 to 7.4. Water  
35 was topped up to 1.0 litre, and the solution was sterile filtrated.



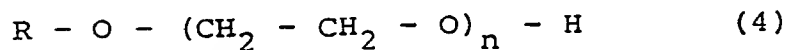
Shaking tests like in example 1 demonstrated that the stability only lasted for 200 hours.



P a t e n t   C l a i m s  
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- 5     1. A stable aqueous, therapeutic insulin preparation  
suitable for use in insulin delivery devices,  
c h a r a c t e r i z e d   in that the aqueous medium  
has a pH of 6.5 to 9 and contains a polyoxyethylene  
alkylether of the general formula

10



- wherein R represents a straight or branched, saturated  
or unsaturated  $C_8 - C_{15}$  alkyl group, and n is an integer  
15   from 2 to 25.

2. An insulin preparation according to claim 1,  
c h a r a c t e r i z e d   in that it contains a compound  
of formula 4 wherein R represents a  $C_{12} - C_{13}$  alkyl group.

20

3. An insulin preparation according to claim 1 or 2,  
c h a r a c t e r i z e d   in that it contains a compound  
of formula 4 wherein n is an integer from 4 to 23, in  
particular 6 to 15.

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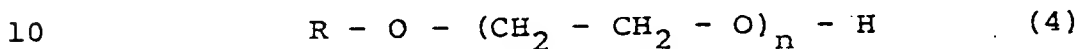
4. An insulin preparation according to claims 1-3,  
c h a r a c t e r i z e d   in that the aqueous medium  
contains human or animal insulin or a derivative thereof  
and, if desired, common additives, such as isotonics,  
30   preservatives, buffers, etc., and optionally also a  
component causing the effect of the preparation to be  
accelerated or protracted.

5. An insulin preparation according to claims 1-4,  
35   c h a r a c t e r i z e d   in that it contains human  
or animal insulin in a concentration of up to 1500 IU/ml.



6. An insulin preparation according to claims 1-5, characterized in that it contains at least 2 ppm of a compound of formula 4.

5 7. A process for preparing an insulin preparation according to claim 1, characterized by admixing an aqueous medium containing insulin with a polyoxyethylene alkylether of the formula



wherein R and n are as defined in claim 1, and, if necessary, adjusting the pH of the medium to 6.5 to 9, and, if desired, adding any residual components of the  
15 medium and/or adjusting the insulin concentration to provide the finished preparation.

8. A process according to claim 7, characterized by adding a compound of formula 4 wherein R  
20 represents a  $C_{12} - C_{13}$  alkyl group.

9. A process according to claim 7 or 8, characterized by adding a compound of formula 4 wherein n is 4 to 23, in particular 6 to 15.

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10. A process according to claims 7-9, characterized by adding at least 2 ppm of a compound of formula 4.



## AMENDED CLAIMS

(received by the International Bureau on 06 December 1982 (06.12.82))

1. (Amended) A stable aqueous, therapeutic insulin  
5 preparation for use in insulin delivery devices,  
c h a r a c t e r i z e d in that the aqueous medium  
has a pH of 6.5 to 9 and contains up to 1000 ppm of a  
polyoxyethylene alkylether of the general formula.

10 
$$R - O - (CH_2 - CH_2 - O)_n - H \quad (4)$$

wherein R represents a straight or branched, saturated  
or unsaturated  $C_8 - C_{15}$  alkyl group, and n is an integer  
from 2 to 25.

15

2. An insulin preparation according to claim 1,  
c h a r a c t e r i z e d in that it contains a  
compound of formula 4 wherein R represents a  $C_{12} - C_{13}$   
alkyl group.

20

3. An insulin preparation according to claim 1 or 2,  
c h a r a c t e r i z e d in that it contains a  
compound of formula 4 wherein n is an integer from 4  
to 23, in particular 6 to 15.

25

4. An insulin preparation according to claims 1-3,  
c h a r a c t e r i z e d in that the aqueous medium  
contains human or animal insulin or a derivative  
thereof and, if desired, common additives, such as  
30 isotonics, preservatives, buffers, etc., and optionally  
also a component causing the effect of the preparation  
to be accelerated or protracted.

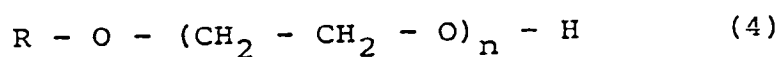
5. An insulin preparation according to claims 1-4,  
35 c h a r a c t e r i z e d in that it contains human or  
animal insulin in a concentration of up to 1500 IU/ml.



6. An insulin preparation according to claims 1-5, characterized in that it contains at least 2 ppm of a compound of formula 4.

- 5 7. (Amended) A process for preparing an insulin preparation according to claim 1, characterized by admixing an aqueous medium containing insulin with up to 1000 ppm of a polyoxyethylene alkylether of the formula

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wherein R and n are as defined in claim 1, and, if necessary, adjusting the pH of the medium to 6.5 to 9,  
15 and, if desired, adding any residual components of the medium and/or adjusting the insulin concentration to provide the finished preparation.

8. A process according to claim 7, characterized  
20 i z e d by adding a compound of formula 4 wherein R represents a C<sub>12</sub> - C<sub>13</sub> alkyl group.

9. A process according to claim 7 or 8, characterized  
t e r i z e d by adding a compound of formula 4  
25 wherein n is 4 to 23, in particular 6 to 15.

10. A process according to claims 7-9, characterized  
t e r i z e d by adding at least 2 ppm of a compound of formula 4.





## STATEMENT UNDER ARTICLE 19

Claim 1 has been amended to limit the claimed stable aqueous insulin preparations to the use in insulin delivery devices and hence exclude possible other administration routes e.g. nasal, rectal, oral or by injection. The amount of polyoxyethylene alkylether in claims 1 and 7 has been limited in accordance with page 5, line 6.

These amendments are intended to avoid cited DE-A-2 620 446 and 2 620 483 as well as Chem. Abstr. Vol. 86 (1977) abstract no. 177336r.



## INTERNATIONAL SEARCH REPORT

International Application No. PCT/SE82/00066

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

A 61 K 37/26

## II. FIELDS SEARCHED

## Minimum Documentation Searched \*

Classification System	Classification Symbols
IPC 2, 3	A 61 K 37/26, 9/08
IPC 1	A 61 k 17/02
US Cl	424:110, 178; :260:112.7

Documentation Searched other than Minimum Documentation  
to the extent that such documents are included in the fields searched \*

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>14</sup>

Category *	Citation of Document, <sup>15</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
X	DE, A, 2 620 446 (TAKEDA CHEMICAL INDUSTRIES LTD) 3 March 1977, see inter alia pages 9, 10 and 13.	
X	DE, A, 2 620 483 (TAKEDA CHEMICAL INDUSTRIES LTD) 23 December 1976, see inter alia pages 4, 7 and 11. & US, A, 4 153 689	
A	DE, A, 2 641 819 (YAMANOUCHI PHARMACEUTICAL CO., LTD) 7 April 1977, see inter alia pages 8 and 9.	
X	DE, A, 2 917 535 (HOECHST AG) 6 November 1980, see inter alia pages 5-6. & EP, A, 0 018 609	
A	US, A, 4 164 573 (ALVIN M GALINSKY) 14 August 1979	
X	Chemical Abstracts, Vol 86 (1977), abstract No 177336r, Japan. Kokai 77 25,013	
A	Journal of Pharmacy and Pharmacology, Vol 32, issued 1980 (London), K Ichikawa	.../...

\* Special categories of cited documents: <sup>16</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search \*

1982-09-29

Date of Mailing of this International Search Report \*

1982-10-05

International Searching Authority \*

Swedish Patent Office

Signature of Authorized Officer <sup>19</sup>

*Martin E. Hjalmsdahl*  
Martin E. Hjalmsdahl

## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 14 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No 18
PX	et al, "Rectal absorption of insulin suppositories in rabbits", see pages 314-318.  International Journal of Pharmaceutics, Vol 9, No 2, issued August 1981 (Elsevier/North-Holland Biomedical Press, Amsterdam), S Hirai et al, "Effect of surfactants on the nasal absorption of insulin in rats", see pages 165-172, especially page 168 and page 165, lines 8-4 from the bottom.	
PX	International Journal of Pharmaceutics, Vol 9, No 2, issued August 1981 (Elsevier/North-Holland Biomedical Press, Amsterdam), S Hirai et al, "Mechanisms for the enhancement of the nasal absorption of insulin by surfactants", see pages 173-184, especially pages 178-179 and 173, lines 9-5 from the bottom.	
P	Journal of Pharmacy and Pharmacology, Vol 33, No 11, issued November 1981 (London), M S Mesha & H I El-Bitar, "Hypoglycaemic effect of oral insulin preparations containing Brij 35, 52, 58 or 92 and stearic acid", see pages 733-734.	